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Optimal dose and type of exercise to improve cognitive function in older adults: A systematic review and bayesian model-based network meta-analysis of RCTs☆

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ABSTRACT

Objective: To examine the dose-response relationship between overall and specific types of exercise with cognitive function in older adults.
Design: Systematic Review and Bayesian Model-Based Network Meta-Analysis.
Data sources: Systematic search of MEDLINE, Web of Science, Scopus, PsycINFO and SPORTDiscus.
Eligibility criteria for selecting studies: Randomized controlled trials of exercise interventions in participants aged 50 years or over, and that reported on at least one global cognition outcome.
Results: The search returned 1998 records, of which 44 studies (4793 participants; 102 different effect sizes) were included in this review with meta-analysis. There was a non-linear, dose-response association between overall exercise and cognition. We found no minimal threshold for the beneficial effect of exercise on cognition. The estimated minimal exercise dose associated with clinically relevant changes in cognition was 724 METs-min per week, and doses beyond 1200 METs-min per week provided less clear benefits. We also found that the dose-response association was exercise type dependent, and our results show that clinically important effects may occur at lower doses for many types of exercise. Our findings also highlighted the superior effects of resistance exercises over other modalities.
Conclusions: If provided with the most potent modalities, older adults can get clinical meaningful benefits with lower doses than the WHO guidelines. Findings support the WHO recommendations to emphasise resistance training as a critical component of interventions for older adults.

1. Introduction

Dementia is one of the major causes of disability and dependency among older people worldwide (Martin et al., 2015). It is an ageing-associated condition characterised by deteriorating cognitive function (Martin et al., 2015). Today, over 46 million people live with dementia, and this will almost double every 20 years, reaching 75 million in 2030 and 131.5 million in 2050 (Martin et al., 2015). Given the epidemic scale of dementia in an ageing population, with no known cure on the horizon, prevention of dementia is one of the greatest public health challenges of the 21st century (Frankish and Horton, 2017).

Physical activity and exercise may help prevent dementia. Physical activity is *'any bodily movement produced by the contraction of skeletal muscles that results in a substantial increase in caloric requirements over resting energy expenditure'* (Caspersen et al., 1985) and includes activities like gardening, shopping, and housework. In contrast, exercise is *'a type*

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of physical activity consisting of planned, structured, and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness' (Caspersen et al., 1985). Both have been well studied for their ability to improve cognitive performance by stimulating molecular mechanisms such as brain-derived neurotrophic growth factor (Vedovelli et al., 2017), learning (Winter et al., 2007), and memory (Wheeler et al., 2020). Because interventions have tended to focus on increased planned, structured activities, they tend to use 'exercise' rather than physical activity. Several systematic reviews and meta analyses (Huang et al., 2021; Northey et al., 2018; Sanders et al., 2019; Turner et al., 2021) have demonstrated the benefits of exercise to improve the global cognition of older adults that are dementia-free (Sanders et al., 2019) and those diagnosed with mild cognitive impairment or dementia (Huang et al., 2021; Sanders et al., 2019). Not surprisingly, clinical (Livingston et al., 2020) and public health guidelines (Erickson et al., 2019) often recommend physical activity and exercise as cornerstone strategies for the prevention and treatment of dementia. The World Health Organization (WHO) recommends that older adults engage in 150—300 min of moderate-intensity aerobic physical activity per week, or 75—150 min of vigorous-intensity aerobic physical activity, and, at least, three times a week of muscle-strengthening activities involving major muscle groups (Bull et al., 2020).

However, there are two major knowledge gaps in the literature that may compromise the ability of healthcare providers to use exercise as 'medication' for healthy cognitive aging. First, the relationship between exercise and cognition may be dependent on the type of exercise being employed (Barha et al., 2017). Although the majority of research has focused exclusively on aerobic exercise (e.g., walking or running), resistance exercise may also enhance cognitive and brain outcomes in older adults (Northey et al., 2018; Turner et al., 2021). Other studies suggest that the greatest cognitive function improvements are obtained through dance (Klimova and Dostalova, 2020) or mind-body (Biazus-Sehn et al., 2020) activities. An emerging literature also highlights the benefits of multicomponent exercise interventions to improve the global cognition of older adults (Carvalho et al., 2021; Huang et al., 2021). A recent network meta-analysis (Huang et al., 2021) with 71 trials and 5606 participants revealed that multicomponent exercise was the most effective to improve cognition among patients with mild-cognitive impairment (MCI) whereas resistance exercise was best for those with established dementia. Meta-analyses have not yet identified the most efficient type of exercise to improve cognitive function in older adults who do not yet have cognitive impairments (e.g., dementia). Sex and obesity status may further influence the relationship between exercise and cognition. For instance, previous studies have also identified superior effects of exercise on cognition among older women compared to older men (Colcombe and Kramer, 2003; Barha et al., 2019), which supports the hypothesis that biological sex may be a potential moderator of the dose-response relationship between exercise and cognition (Barha and Liu-Ambrose, 2018; Barha et al., 2019). An obesity-induced cognitive impairment has also been demonstrated (Balasubramanian et al., 2021) and a systematic review of randomized controlled trials (Chang et al., 2017) indicated that obesity status may moderate the associations between exercise and cognition. In addition, the dose-response relationship is critical to explore, as flagged by the WHO's physical activity and sedentary behaviour Guidelines Development Group in 2020 (Bull et al., 2020) and the 2018 US Physical Activity Guidelines Advisory Committee (Erickson et al., 2019). This information is key to establishing the minimal effective and optimal doses and maximum safety threshold of exercise to improve the cognitive function of older adults (Bull et al., 2020).

Two reviews have assessed this dose-response relationship (Sanders et al., 2019; Groot et al., 2016). Among older adults with cognitive impairment, high-dose interventions (defined at >150 min/week) were no more effective than low-dose ones (<150 min/week; Groot et al., 2016). Sanders et al. (2019) also found that the total dose did not matter, but suggested that shorter, more frequent exercise was better. For those without cognitive impairments, dose did not appear to influence response (Sanders et al., 2019). However, both reviews generally treated dose—which is continuous—as categorical (e.g., 'long' sessions were >45 min). This can hide true dose-response effects because the method treats all interventions within a category as equivalent (e.g., treats a 45-minute session the same as a 200-minute session). When reviews did allow for continuous moderation (e.g., total dose in Sanders et al., 2019), they used linear models which could not account for plausible 'goldilocks zones', where too low a dose is ineffective but too high leads to drop-out. Finally, they could not easily model the dose-response curves for different modalities of exercise (e.g., resistance vs. aerobic).

Capitalizing on novel meta-analytic techniques (i.e., model-based dose-response network meta-analysis under a Bayesian framework) and evidence stemming from existing RCTs, the current report examined the dose-response relationship between exercise dose and cognitive function in older adults with and without mild cognitive impairment. We investigated the influence of exercise modality, obesity, cognitive status, and sex on these dose-response associations (Barha et al., 2017; Kuo et al., 2006; Mewborn et al., 2017; van Exel et al., 2001). To enhance the clinical interpretation of our study, we additionally estimated the minimal dose for each type of exercise necessary to achieve a minimal clinically important difference (MCID) in cognitive function.

2. Methods

This pre-registered systematic review with meta-analysis (PROSPERO reference number #CRD420202191039) was reported following the PRISMA checklist (Page et al., 2020).

2.1. Search strategy

We conducted a systematic search in MEDLINE, Web of Science (WOS), Scopus, PsycINFO and SPORTDiscus from inception to December 2021. The specific search strategies, including search terms, dates, and process, are shown in Supplementary File 1. The reference lists of relevant articles and reviews were also screened for additional studies. Title/abstract and full-text screening were conducted independently and in duplicate by investigators (DGG and FAB), with disagreements resolved by discussion or adjudication by a third author (JdPC).

2.2. Selection criteria

We included (1) randomized controlled trials that (2) were written in English, and (3) used any type of exercise as intervention. (4) To be considered, studies had to include a control group that received no exercise intervention; (5) had to report on at least one global cognition outcome; and (6) had to include participants aged 50 years or over (Erickson et al., 2019; Northey et al., 2018). We excluded studies that reported on the acute effects of exercise or that mixed different interventions (e.g., exercise plus cognitive therapy) to ensure that the effects on cognitive function were due to exercise. We also excluded studies with participants diagnosed with dementia and studies focusing on particular health conditions or clinical populations.

2.3. Data extraction

Two authors independently extracted data from studies that met the inclusion criteria (DGG and FAB) and disagreements were resolved by consensus between all authors. From each of the included studies, we extracted whether participants had MCI diagnosis, body mass index (BMI), sex, intervention and control description, cognitive evaluation tool, and any data that could be used to calculate effect sizes. When the minimally required data to conduct the dose-response meta-analysis could not be retrieved from the published reports(Bademli et al., 2019; Canli and Ozyurda, 2020; Cavalcante et al., 2020; Choi and Lee, 2019;

Frändin et al., 2016; Liao et al., 2019; Singh et al., 2014), we contacted the authors and invited them to provide additional data. Of these 7 studies, authors of 5 studies were able to provide the data we required.

2.4. Data coding and management

We classified the interventions into four hierarchical levels: First, interventions were coded as "Exercise" or "Control" (first level). At class level (second level), the interventions were coded according to their main exercise type: "Resistance Training", "Aerobic Training", "Mixed Physical Activity" and "Control". At the third level, the interventions were coded according to the specific type of exercise performed: "Resistance bands", "Body-and-free weight and machines", "Walking", "Cycling", "Mixed Aerobic Exercises" (i.e., swimming, dancing, mind-body exercises), "Aerobic and resistance exercises" (i.e., concurrent training), "Aerobic, resistance and balance exercises", "Resistance and balance exercises" and "Placebo" (as control). Finally, interventions were coded at the intersection of specific type and dose—defined as the energy expenditure (i.e., Metabolic Equivalent of Task, MET) that results from the product of the duration, frequency, and intensity of a certain type of exercise (Ainsworth et al., 2011; Wasfy and Baggish, 2016); and expressed as METs-min per week. For example, 500 METs-min per week of "Resistance bands". Next, we clustered the interventions into five different groups by approximating the estimated METs-min per week to the closest convenient pre-specified grouping categories of 0 (control group), 500, 750, 1000 or 2000 METs-min per week. This approximation was done in order to facilitate the network connectivity, a necessary step to conduct the network meta-analysis (Higgins et al., 2012). The final analytical dataset is shown in Supplemental File 2.

2.5. Data synthesis

We used a random-effects Bayesian Model-Based Network Meta-Analysis (MBNMA) (Mawdsley et al., 2016) to summarize the dose-response association between exercise dose and cognition. No indication of violation of key assumptions for network meta-analysis (i.e., connectedness of the network (Veer et al., 2019), consistency in the data, and transitivity (Wheeler et al., 2010; White et al., 2012)) was found (Supplementary File 3). All effect sizes were reported as standardized mean differences (SMD; Hedges'g(Hedges and Olkin, 1985)), and 95% credible intervals (CrI) were used to assess the credibility of our estimates (Etzioni and Kadane, 1995).

First, we plotted the observed effects of different physical activity types and doses on cognition. Based on the observed shapes, a range of recommended non-linear functions (i.e., Emax, restricted cubic splines, quadratic, and non-monotonically up (Pedder et al., 2019)) were used to model the data. Next, we derived and compared different fit indices (Evans, 2019) (i.e., Deviance Information Criterion (DIC), between-study standard deviation, number of parameters in the model, residual values) as well as corresponding deviance plots (Evans, 2019) across models (Supplementary File 4). Restricted cubic splines yielded the best fit in all cases and were therefore used to assess the non-linear dose-response associations (Supplementary File 4). According to the model with the best fit (Supplementary Table 2) and biological plausibility (Pedder et al., 2019), we placed three knots at the 10th, 50th and 90th percentile of the exercise dose (energy expenditure) (Hamza et al., 2021; Harrell, 2001). Departure from linearity was assessed using a Wald test (Hamza et al., 2021; Harrell, 2001). Beta coefficients from the restricted cubic splines were used to estimate the physical activity dose at which the predicted maximal significant effect on cognition was achieved. This information was used to rank the type of physical activity and exercise based on their probability to elicit changes on cognitive function, from worst to best.

To further enhance the clinical utility of our results, we estimated the dose (or range of doses) at which interventions were able to achieve the minimum clinically important difference (MCID) (Bernstein and Mauger, 2016) for cognitive function. In this analysis, we only used studies that evaluated cognitive function through the Mini-Mental State Examination (MMSE) (Folstein et al., 1983) (i.e., majority of effect sizes, 53/102). The MMSE has shown a robust predictive validity in the population of interest (Mitchell, 2013). Following existing methods (Watt et al., 2021), we used a distribution-based approach to derive a pooled MCID for MMSE, estimated to be 1.6 points in this study. We then calculated the pooled effect size (SMD) of the studies that at least achieved the estimated pooled MCID ($k = 12$). Finally, we predicted at which dose(s) of exercise these effects were achieved for overall and for each type of intervention.

To explore the potential influence of MCI diagnosis, BMI, and sex (Kuo et al., 2006; Mewborn et al., 2017; van Exel et al., 2001) on the calculated dose-responses association between exercise effects and cognitive function, we used a flexible approach that integrates meta classification and regression trees (meta-CART) (Dusseldorp et al., 2014; Li et al., 2020). This approach has been shown to improve the recognition of influential covariates, particularly in the presence of multiple moderators (Dusseldorp et al., 2014; Li et al., 2020, 2017; Spineli and Pandis, 2020). Missing data on covariates was managed through multiple imputation with chained equations (n imputations = 20) (Ellington et al., 2015). For statistically significant first-node covariates (P-value <0.05), we plotted the dose-response relationships separately for each of the levels of the covariate of interest.

All analyses were performed in R 4.0.3 (R Core Team , 2021). We used the '*metafor*' package (Viechtbauer, 2010) to calculate effect sizes treatments (Hedges'g); the '*MBNMAdose*' package(Pedder, 2021) to perform MBNMA and dose-response relationships; the '*metacart*' package (Dusseldorp et al., 2014; Li et al., 2017) for decision-trees meta--analysis modeling; and the '*ggplot2*' package (Wickham, 2011) for dose-response curves plotting and visualization. The code necessary to reproduce the results presented in this manuscript are available through the GitHub account of the first author (URL: https://github.com/dg-algom/Physical-Activity-and-Cognitive-Function-Dose-response-Model-Based-Network-Meta-Analysis/blob/main/.github/workflows/blank.yml).

2.6. Risk of bias and quality of evidence

Three reviewers (DG, BdPC, and RMA) assessed and rated the studies according to the Cochrane Risk of Bias Tool (Higgins et al., 2011) (Cochrane ROB Tool) criteria. We conducted a sensitivity analysis excluding studies with high-risk bias to determine if these studies accounted for significant variance in the overall dose-response estimates. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to rate the quality of evidence (Kavanagh, 2009).

3. Results

3.1. Characteristics of included studies

We identified 1998 potentially eligible studies through the initial electronic searches. After screening citations by title and abstract, we considered 139 potentially eligible studies for inclusion and retrieved full-text articles. After removing duplicates and applying the inclusion criteria, 44 studies (Ansai and Rebelatto, 2015; Bademli et al., 2019; Bell et al., 2019; Cancela Carral and Ayán Pérez, 2007; Canli and Ozyurda, 2020; Carta et al., 2021; Cavalcante et al., 2020; Cherup et al., 2018; Choi and Lee, 2019; Dorner et al., 2007; Espeland et al., 2017; Farinha et al., 2021; Ferreira et al., 2018; Frändin et al., 2016; Hewitt et al., 2018; Hong et al., 2018; Htut et al., 2018; Inoue et al., 2018; Khanthong et al., 2021; Kitazawa et al., 2015; Lam et al., 2015; Langoni et al., 2019; Langlois et al., 2013; Lautenschlager et al., 2008; Law et al., 2019; Lü et al., 2016; Cardalda et al., 2019; Moul et al., 1995; Muscari et al., 2010; Qi et al., 2019; Ruiz et al., 2015; Suzuki et al., 2012; Ikai et al., 2013; Tao

et al., 2019; Tarazona-Santabalbina et al., 2016; Timmons et al., 2018; Varela et al., 2012; Venturelli et al., 2010; Wang et al., 2020; Wei and Ji, 2014; Williamson et al., 2009; Yoon et al., 2017; Zhu et al., 2018; Zotcheva et al., 2021) (4793 participants; 102 different effect sizes) were selected for inclusion in the meta-analysis (Fig. 1).

The characteristics of included studies are shown in Supplementary File 5. The year of publication ranged from 1995 and 2021. A total of 2806 (58.54%) participants were women. The mean reported age was ~74 (SD = 6.58) years old. There were 2410 (44.78%) older adults diagnosed with mild cognitive impairment, and 2228 (54.22%) older adults were classified as overweight or obese based on their BMI.

3.2. Dose-response relationships

Fig. 2 shows the non-linear dose-response association between exercise dose and cognition. The effects of overall exercise on cognitive function markedly increased up to about 1200 METs-min (linear slope = 0.14 for every 100 METs-min). Beyond 1200 METs-min only marginally increased the magnitude of effects (linear slope = 0.06 for every 100 METs-min), although no evidence of apparent plateauing of the relationship was evident within the predicted variation in the exposure. Predicted effects were moderate for 600 METs-min (i.e., the equivalent in energy expenditure of the lower bound of WHO recommended level of physical activity (Bull et al., 2020); Hedges' g = 0.79; 95% CrI [0.61, 1.11]; SD = 0.10) and large for 1200 METs-min (i.e., the equivalent in energy expenditure of the upper bound of WHO recommended level of physical activity (Bull et al., 2020); Hedges' g = 1.53; 95% CrI [1.17, 1.95]; SD = 0.20) and 1800 METs-min (i.e., the equivalent in energy expenditure of double the minimum WHO recommended level of physical activity (Bull et al., 2020); Hedges' g = 1.91; 95% CrI [0.89, 2.98]; SD = 0.57).

Fig. 3 shows the dose-response curve for each type of intervention analysed in this study. We detected an inverted U-shaped dose-response relationship between exercise dose and cognition for aerobic and resistance exercises and for resistance bands. Predicted maximal significant responses were observed at 601 METs-min for aerobic and resistance exercises (Hedges'g = 1.44; 95% CrI [0.69, 2.13]; SD = 0.37) and 376 METs-min for resistance bands (Hedges'g = 2.98; 95% CrI [1.50, 4.19]; SD = 0.60). Doses beyond 1030 METs-min for aerobic and resistance exercises and 679 METs-min for resistance bands resulted in non-significant effects.

Non-linear positive dose-response associations were found for body-and-free weights and machines, mixed aerobic exercises, and walking. We did not detect a lower threshold for the effectiveness of body-and-free weights and machines and mixed aerobic exercises on cognition, and the maximum effects were achieved with 891 and 1800 METs-min

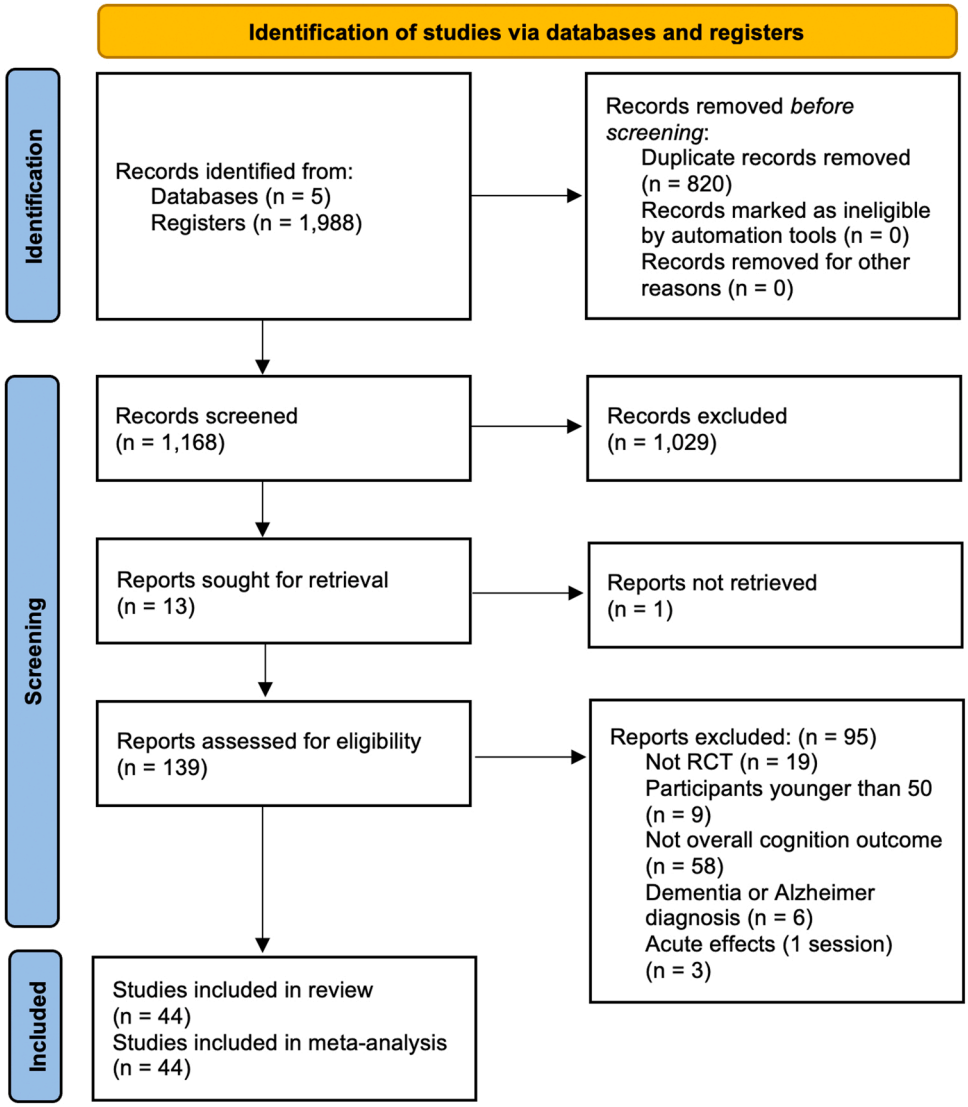

Fig. 1. PRISMA flow diagram of study selection.

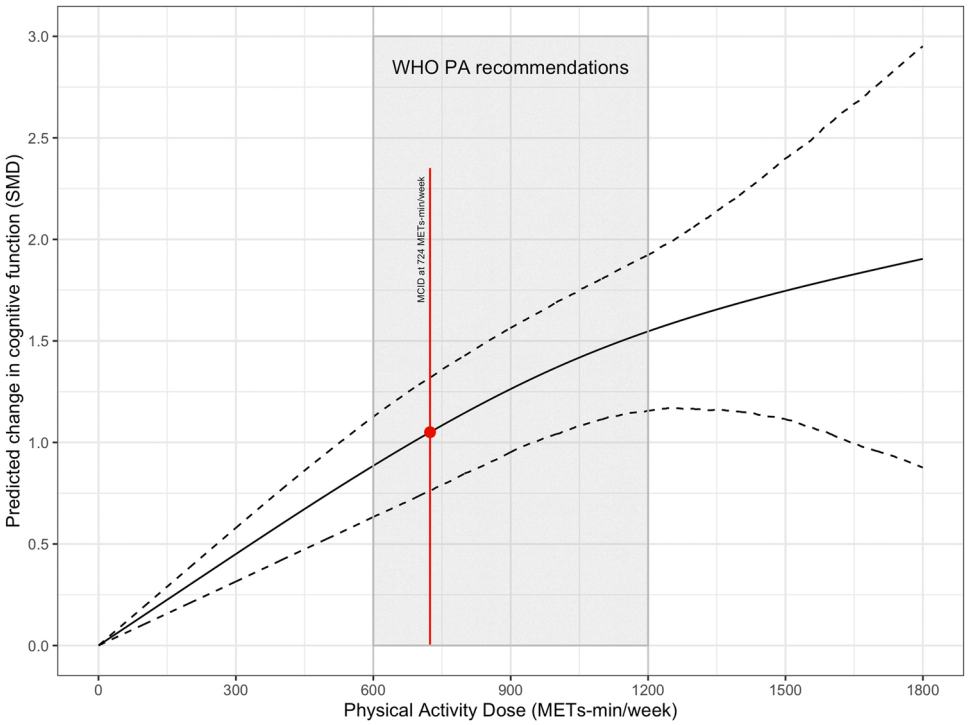

Fig. 2. Dose-response association between overall physical activity dose and change in cognitive function in older adults. *P*-value from the second spline = 0.032.

per week for body-and-free weights and machines and mixed aerobic exercise respectively. Significant effects were found between 557 (Hedges' g = 0.66; 95% CrI [0.01, 1.35]; SD = 0.34) and 851 METs-min per week (Hedges' g = 1.11; 95% CrI [0.01, 2.08]; SD = 0.55) for walking. No significant associations were observed for cycling and resistance and balance exercises, whereas a minimal dose of 836 METs-min was needed to elicit significant changes in cognition for aerobic, resistance and balance exercises modality (Hedges'g = 0.99; 95% CrI [0.01, 1.87]; SD = 0.48). Given the a priori similar mechanisms of action, we clustered all types of resistance exercise interventions (i.e., body-and-free weights and machines, resistance and balance exercises, and resistance bands) and calculated their combined dose-response relationship with cognition, which shows an inverted U-shaped association (Fig. 3).

Supplementary File 6 shows the predicted effects for the lower and upper bound of WHO recommended level of physical activity(Bull et al., 2020) as well as corresponding effects for double the minimum WHO recommended level of physical activity(Bull et al., 2020). Our ranking analysis shows that resistance bands had the highest probability of producing the greatest results on cognition (Supplementary File 7).

3.3. Exercise dose and Minimal Clinically Important Difference

The pooled effect size equivalent to the estimated MCID for MMSE was large (Hedges' g = 1.05; 95% Confidence Intervals [0.47, 1.63]; SE = 0.3) and the minimal predicted dose of exercise needed to achieve this effect was 724 METs-min per week. Corresponding values were 293–928 METs-min for aerobic and resistance exercises, 872 METs-min for aerobic, resistance and balance exercises, 529–891 METs-min for body-and-free weights and machines, 758 METs-min for mixed aerobic exercises, 78–679 METs-min for resistance bands, 796–851 METs-min for walking, and 474–777 METs-min for resistance exercise cluster. Table 1 presents practical recommendations for exercise advice based on these estimations.

3.4. Influence of MCI, BMI status, and sex

The meta-CART model ($k = 52$; $tau^2 = <0.001$; *P*-value = 0.003) revealed that BMI status significantly influenced the dose-response association between exercise dose and cognition; and MCI and sex were secondary moderators of this relationship (i.e., significant second-node moderators after BMI status). The resulting meta-tree with the subgroup meta-analysis results are shown in Supplementary File 8. We found an upward, non-linear dose-response association for participants with healthy BMI ($k = 21$; pooled mean effect Hedges' g = 1.29; 95% CI [0.72, 1.85]; SE = 0.29). In contrast, an inverted U-shaped dose-response relationship between exercise dose and cognition was found for overweight/obese individuals ($k = 31$; pooled mean effect Hedges' g = 0.52; 95% CI [0.33, 0.71]; SE = 0.01). In this group, the maximal significant response was predicted at 634 METs-min per week ($k = 31$, Hedges' g = 0.97; 95% CrI [0.51, 1.37]; SD = 0.24), and doses beyond 1053 METs-min per week resulted in non-significant effects. Both dose-response relationships are illustrated in Fig. 4.

3.5. Risk of bias and quality of evidence

Sixteen studies had low-risk of bias, eighteen studies had some risk of bias, and ten studies had high-risk of bias (Fig. 5). Study-level risk of bias assessment is shown in Supplementary File 9. Sensitivity analysis conducted including only low risk of bias studies yielded consistent results compared with the main analysis (Supplementary File 10). The minimal dose necessary to achieve a clinically relevant change in cognition increased to ~1075 METs-min per week after excluding studies with higher risk of bias. According to the GRADE system, the overall quality of the evidence was moderate.

4. Discussion

For the first time, this dose-response meta-analysis shows a non-linear relationship between exercise and cognition in older adults. The current study has several key findings with important clinical and public health implications. First, we found no minimal threshold for the

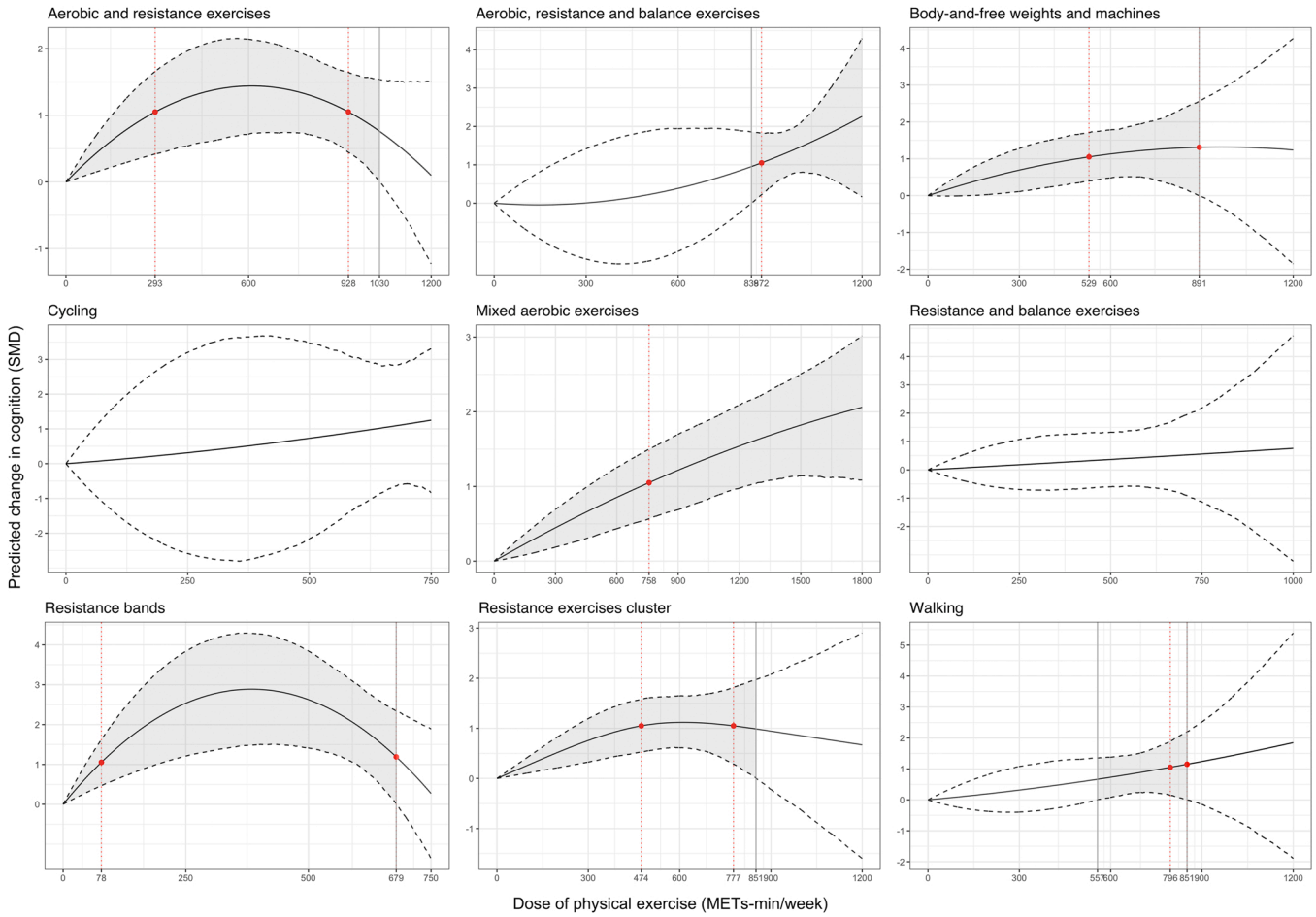

Fig. 3. Dose-response associations between different types of physical activity and exercise doses and change in cognitive function. *P*-values from the second spline were 0.040 for aerobic and resistance exercises; 0.045 for aerobic, resistance and balance exercises; 0.033 for body-and-free weights and machines; 0.040 for cycling; 0.009 for mixed aerobic exercises; 0.022 for resistance and balance exercises; < 0.001 for resistance bands; 0.017 for cluster resistance exercise; and < 0.001 for walking.

beneficial effect of exercise on cognition, which echoes the 'doing some physical activity is better than doing none' statement from the 2020 WHO guidelines on physical activity and sedentary behaviour (Bull et al., 2020). Second, the estimated minimal exercise dose associated with clinically relevant changes in cognition in this study (i.e., 724 METs-min per week) is slightly above the lower bound of WHO recommended level of physical activity (i.e., 600 METs-min per week; equivalent to 150 min/week of moderate intensity or 75 min/week of vigorous activity) (Bull et al., 2020). This finding is particularly relevant because 724 METs-min per week may be an achievable target with substantial health benefits for many older adults, which may be particularly encouraging for the most inactive group. Third, the additional benefits beyond the upper bound of WHO recommended level of physical activity—that is, exercise beyond 1200 METs-min per week (i.e., the equivalent to 300 min/week of moderate intensity activity or 150 min/week of vigorous activity) (Bull et al., 2020) may provide less clear benefits for cognition. These observations support the current WHO guidelines for physical activity in older adults, and for cognitive health (Bull et al., 2020). Lastly, we were able to ascertain specific dose-response associations for a range of different types of exercise. Taken together, our findings provide an opportunity to inform future exercise guidelines aimed to improve the global cognition of older adults and reduce the burden associated with dementia amongst this ever-increasing segment of the population.

An interesting finding of this study was that obesity status was the main moderator of the effects of exercise on cognition. Our results suggest that overweight/obese older adults may benefit from lower exercise levels than the recommended for the general population. For example, the predicted dose at which the maximum effect was observed for this subgroup was ~600 METs-min per week; and doses beyond ~1000 METs-min per week resulted in predicted null cognitive improvements. Previously reported high levels of sedentary behavior in obese individuals (Di Francesco et al., 2005; Zbronska and Medrela-Kuder, 2018) coupled with possibly lower levels of fitness (Prakash et al., 2011; Wong et al., 2015) may partly explain these observations. Higher doses may reflect unrealistic goals for previously sedentary individuals. Our results may also indicate the need to progressively build up the exercise level recommendations for this particular subgroup of older adults.

Notably, we found that the dose-response association was intervention-specific; and detected two clear patterns on these associations. On one hand, aerobic and resistance exercises and resistance bands followed an inverted U-shape relationship. In contrast, body-and-free weights and machines, mixed aerobic exercises and walking followed non-linear, positive relationships. Interestingly, when all resistance physical activities were clustered together, we observed an inverted U-shape relationship with cognition. These differences align well with previous research (Huang et al., 2021; Northey et al., 2018; Sanders et al., 2019); and highlight the benefits of our methods to assess non-linear dose-response effects, moderated by exercise type. The findings may reflect the different mechanisms and pathways of action through which different exercise types elicit changes in cognition (Bliss

Table 1
Exercise recommendations to improve cognitive function in older adults.

Type of physical activity	MCID (METs-min/ week)	Intensity	Energy expenditure[a] (METs-min)	Recommended accumulation (min/ week)		Recommendations for exercise prescription[b] (sessions x mins/ per week)	
				Minimum[c]	Optimal[d]	Minimum[c]	Optimal[d]
Aerobic and resistance exercises	293 – 928	Moderate	4.3 (code 02035)	~70	~140	3 x ~25 5 x ~15	3 × 45 5 x ~30
		Vigorous	8.0 (code 02032)	~35	~75	2 × 20	2 × 35 3 × 25
Body-and-free weights and machines	529 – 891	Moderate	3.8 (code 02022)	~140	~230	3 x ~40 5 x ~30	5 x ~45
		Vigorous	8.0 (code 02020)	~65	~110	2 × 30	3 x ~35 5 x ~20
Mixed aerobic exercises	758	Moderate	4.3 (mean of codes 02105, 02017, 02120, 02160)	~175	~400	4 x ~45 5 x ~35	7 x ~60
		Vigorous	7.6 (mean of codes 02005, 02110, 02019, 02062)	~95	~240	3 x ~30 4 x ~25	4 × 60 6 × 40
Resistance bands	78 – 679	Moderate	3.5 (code 02054)	~20	~110	2 x ~10	3 x ~35 5 x ~20
		Vigorous	5.0 (code 02052)	~15	~75	1 x ~15 2 x ~20	3 x ~25 5 x ~15
Resistance exercises cluster	474 – 777	Moderate	3.5 (code 02054)	~135	~170	3 x ~45 5 x ~25	3 x ~60 5 x ~35
		Vigorous	6.0 (code 02050)	~80	~100	3 x ~25 5 x ~15	3 x ~35 5 x ~20
Walking	796 – 851	Moderate	4.5 (code 17088)	~175	~190	3 x ~60 5 x ~35	3 x ~65 5 x ~40
		Vigorous	7.0 (code 17230)	~115	~120	3 x ~40 5 x ~25	3 x ~45 5 x ~25

[a] Intensity coding was extracted from the Compendium of Physical Activity (Ainsworth et al., 2011).
[b] Minutes of the main exercise type without considering warm-up and cool-down.
[c] Minimal dose for predicted clinically significant cognitive improvements.
[d] Dose(s) at which the greatest relevant changes in cognition are achieved.

et al., 2021; Herold et al., 2019). Differences in perceived fatigue and effort between exercise modalities may also partly account for our observations. Remarkably, lower doses of resistance exercises were necessary to elicit clinically meaningful changes in cognition compared with aerobic activities. This is in agreement with recent findings that suggest the superior effects of resistance exercise for improving the global cognition of older adults (Huang et al., 2021); and also resonates with our own observations. It is likely that more efficient neuropsychological processes account for this observation (Barha et al., 2017; Voss et al., 2011), or the value of resistance training in maintaining activities of daily living, but future research is warranted to elucidate the specific mechanisms by which resistance exercise may be superior to aerobic exercises for improving cognition of older adults.

This dose-response analysis has several major clinical implications. First, we provide information that can be directly used to inform what dose and type of exercise to recommend for optimal cognitive health among older adults. Second, our findings show that an exercise dose is better than none and suggest that recommendations such as 'every step count' described in the 2020 WHO physical activity guidelines might be a more feasible and efficient recommendation for boosting cognition in older adults. Third, our results also show that clinically important effects may occur at doses of exercise which are significantly below the recommended minimum dose of 600 METs-min per week (Bull et al., 2020), depending on the type of exercise performed (e.g., ~500 METs-min per week for resistance exercises). Furthermore, we were able to identify minimal and optimal doses of a variety of resistance exercises (i.e., body-and-free weights and machines, resistance and balance exercises, and resistance bands), thereby providing improved recommendations than what is currently advised (i.e., three days per week of muscle strengthening activities involving major muscle groups) (Bull et al., 2020). Together, our findings represent an important step towards accurate exercise recommendations aimed to improve the global cognition of older adults. Lastly, the information provided in this manuscript supports tailored exercise advice adapted to individual preferences, needs, and availability of resources (Lange et al., 2019), which may facilitate the adoption of a patient-centered care approach (Constand et al., 2014).

This study has limitations. First, the lack of available data prevented us to assess the dose-response effects of exercise on specific cognitive domains (e.g., memory). Furthermore, this lack may have hampered the ability to provide accurate predictions at the higher end of exercise doses, for which a substantial incremental widening of CrIs was observed. Similarly, there were not enough studies to simultaneously moderate for the different types of exercise and patient characteristics like overweight and obesity. Finally, due to the diversity of cognitive function assessment tools in this meta-analysis, our MCID estimations were limited to studies with MMSE, which may have impacted the generalizability of our estimations. Nonetheless, the previously reported lack of sensitivity of the MMSE to detect small changes in cognition may have obscured the actual effects of interventions on cognition. In addition, the lack of enough powered studies to detect changes in MMSE (i.e., half of included studies in the analysis reported MMSE as a secondary outcome) may have further biased our estimates. There are several key strengths to our study. First, this meta-analysis comprised a relatively large sample size of healthy and older adults, which provided adequate statistical power for the study aims. Second, we applied advanced Bayesian-based meta-analytical techniques for pooling data from different studies to investigate the dose-response between exercise and cognition. This novel method allowed us to determine the 'optimal' exercise dose associated with clinically meaningful changes in cognition, thereby increasing the clinical utility of our results. A key related strength was the ability to ascertain the dose-response for a variety of types of physical activities. Lastly, through estimation of direct and indirect effect sizes and network meta-analysis, we were able to identify and compare the relative efficacy of different interventions. This led to identification of the most effective type of exercise to improve cognition

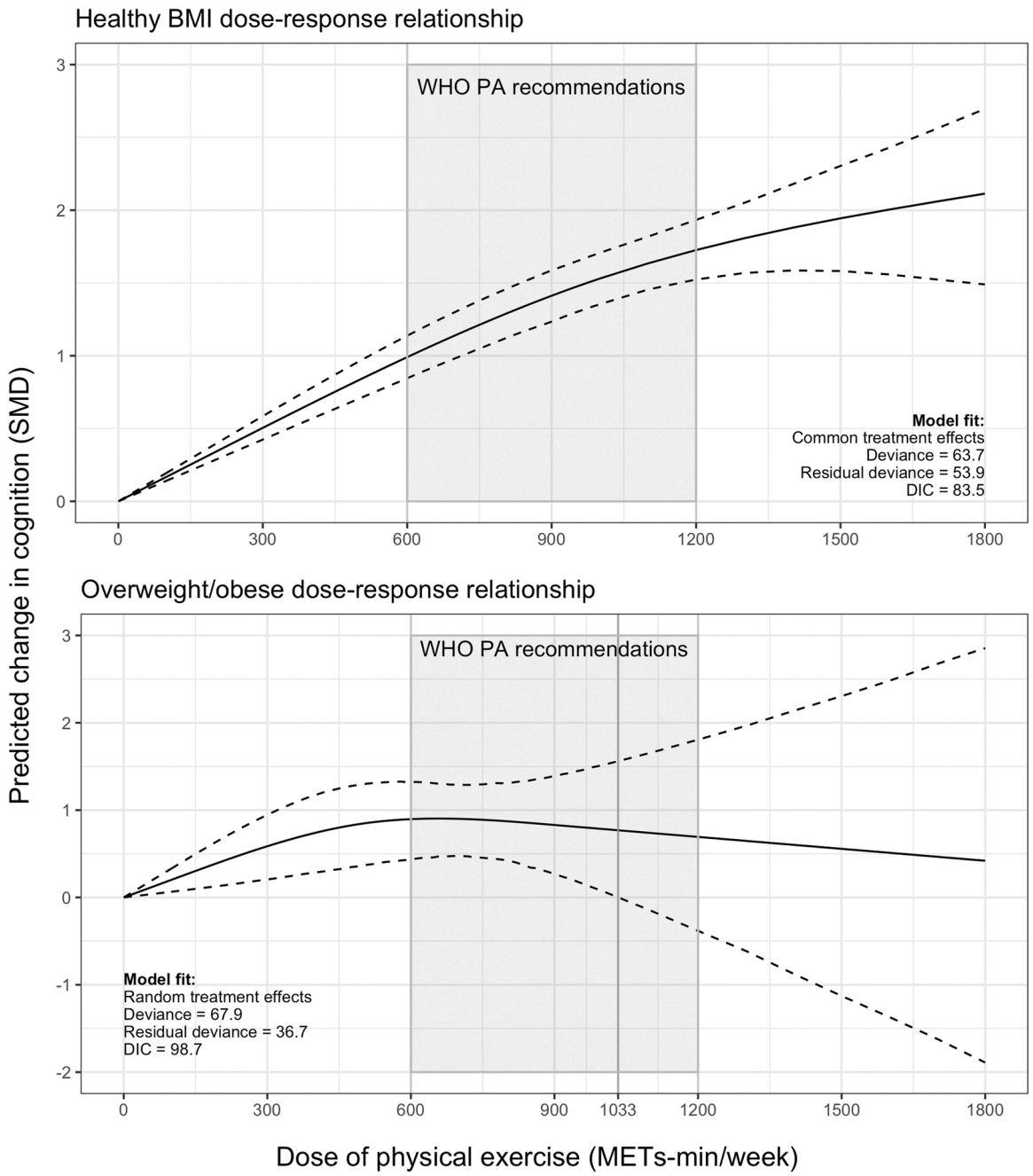

Fig. 4. Dose-response associations between overall physical activity dose and change in cognitive function in older adults with normal weight and overweight/obese. *P*-values from the second spline were 0.032 for participants with normal weight and 0.024 for participants with overweight/obese.

in older adults.

4.1. Conclusions

In conclusion, this systematic review with meta-analysis has identified the dose-response relationship of different types of exercise with cognitive function in older adults. Our results support the clinical utility of low doses of exercise for improving cognition in older adults, especially for resistance training. Exercise is one of the few interventions shown to prevent and treat dementia or cognitive decline in older adults. Using these findings to prescribe exercise wisely could help us better address one of the great public health challenges of the 21st century (Frankish and Horton, 2017).

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Ethical approval information

Not applicable.

CRediT authorship contribution statement

DGG, BdPC, and JdPC conceptualized the study. DGG and BdPC drafted the manuscript; DGG conducted the formal statistical analyses; DGG, FAB, RMR, and MN acquired the data; all authors revised the manuscript and provided critical input. DGG and JdPC had full access to

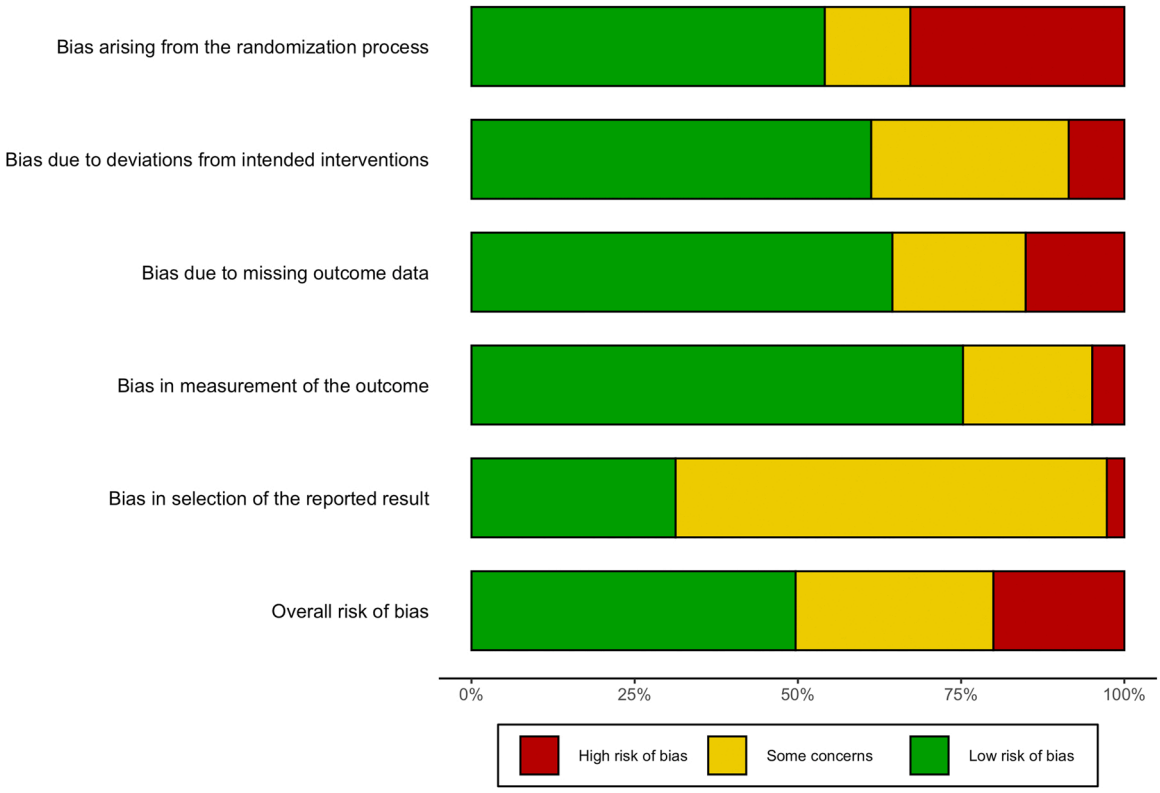

Fig. 5. Cochrane Risk of Bias Tool.

all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Competing Interest

None of the authors declare any conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101591.

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